PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32352A/HO 55	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/01227	International filing date *(day/month/year)* 07.02.2003	Priority date *(day/month/year)* 08.02.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/55		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.07.2003	14.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Markopoulos, E Telephone No. +49 89 2399-8658

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/01227

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	see V.4
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-5 929 067 (VEENSTRA SIEM JACOB ET AL) 27 July 1999 (1999-07-27)

D2: US-B1-6 319 917 (GERSPACHER MARC ET AL) 20 November 2001 (2001-11-20)

D5: RENZI D ET AL: 'Substance P (neurokinin-1) and neurokinin A (neurokinin-2) receptor gene and protein expression in the healthy and inflamed human intestine.' AMERICAN JOURNAL OF PATHOLOGY. UNITED STATES NOV 2000, vol. 157, no. 5, November 2000 (2000-11), pages 1511-1522, XP002240090 ISSN: 0002-9440

D6: GERSPACHER, MARC ET AL: 'Dual neurokinin NK1/NK2 antagonists: N-[(R,R)-(E)-1-arylmethyl-3-(2- oxo-azepan-3-yl)carbamoyl]allyl-N-methyl-3 ,5-bis(trifluoromethyl)benzamides and 3-[N'-3,5- bis(trifluoromethyl)benzoyl-N-arylmethyl-N '-methylhydrazino]-N-[(R)- 2-oxo-azepan-3-yl]propionamides' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(23), 3081- 3084 , 2001, XP002240091

2. Novelty

D1 claims 1-Aryl-2-acylaminoethane compounds (see eg. examples no. 1/18, 19/13, 39/2, 44) like the present application, pharmaceutical compositions thereof and their use as NK-1 receptor antagonists (antagonists of substance P) as well as additionally NK-2 receptor antagonists such as in disorders of the gastrointestinal system like Crohn's disease, diarrhea, and ulcerative colitis (claims 1-9; col. 6 par. 2-3). Specific example no. 42 is matching exactly with the fifth compound on page 5 of the present application.
Hence, claims 1, 3-5 and 7-9 cannot be regarded as novel.
Claim 2 referring to the R configuration at position 4 which is not disclosed in D1 is novel vis-a-vis D1.

Likewise, D2 claims the same compounds (examples, especially example 22) as the present application and their use as NK-1 and NK-2 receptor antagonists such as in disorders of the gastrointestinal system like diarrhea, and ulcerative colitis (column 3, par. 3-4).
Although D2 does not disclose visceral hypersensitivity disorders per se, claims 1-9 are

novelty-destroyed since the mentioned disorders partly overlap with the diseases mentioned in D2. Irritable bowel syndrome (IBS) is not a disease but rather a functional disorder, which means there is an altered physiological function, i.e. that the bowel doesn't work as it should. Diarrhoe is one of the major symptoms of IBS, but also of other disorders. Hence, the mentioned compounds would be used by the skilled man in cases of e.g. diarrhea irrespective of the cause leading to diarrhea.

3. Inventive step

D5 discloses upregulated NK-1R and NK-2R in patients with Crohn's disease and ulcerative colitis and suggests the use of NK-1R and NK-2R antagonists in the treatment of inflammatory bowel disease, especially in treating diarrhea, pain, and inflammation (p. 1520, col. 2, par. 3).

D6 discloses dual neurokinin NK1/NK2 antagonists such as DNK333 aiming at the simplification of the structure and the finding of substances with balanced affinity for both receptors (abstract; p. 3082, col. 1, par. 2 - p. 3084, col. 1, par. 1).

If novelty is restored the following should be observed:

Since epithelial hypersecretion, intestinal motility dysfunction leading e.g. to diarrhea, as well as enteric pain are symptoms of IBD as well as IBS and Crohn's disease and since the use of NK-1R and NK-2R antagonists have a therapeutic effect in these disorders, the subject-matter of claims 1-9 would not be regarded as inventive, moreover since exactly the same compounds have already been cited in the treatment of the above mentioned diseases.

4. For the assessment of the present claims 1-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.